



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 312, 314, 601, 610, 801, 807, 809, 812, and 814

[Docket No. FDA-2006-N-0364]

Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is adopting as a final rule, without change, the interim final rule that issued regulations permitting FDA Center Directors to grant exceptions or alternatives to certain regulatory labeling requirements applicable to human drugs, biological products, or medical devices that are or will be included in the Strategic National Stockpile (SNS). FDA is taking this action to complete the rulemaking initiated with the interim final rule.

DATES: This rule is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of December 28, 2007 (72 FR 73589), FDA issued an interim final rule entitled “Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile” (hereinafter referred to as the interim

final rule).¹ This rule became effective upon the date of publication in the Federal Register.

We issued the interim final rule to facilitate the safety, effectiveness, and availability of appropriate medical countermeasures stored in the SNS in the event of a public health emergency. We also recognized that it may be appropriate for certain human drugs, biological products, or medical devices (hereinafter referred to collectively as medical products) that are or will be held in the SNS to be labeled in a manner that would not comply with certain FDA labeling requirements. However, noncompliance with these labeling requirements could render such products misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 352). Under this rule, the appropriate FDA Center Director may grant exceptions or alternatives to certain regulatory labeling requirements applicable to medical products that are or will be included in the SNS if he or she determines that compliance with the labeling requirements could adversely affect the safety, effectiveness, or availability of specified lots, batches, or other units of medical products that are or will be included in the SNS. An exception or alternative granted under this rule may include conditions or safeguards deemed appropriate by the FDA Center Director to ensure that the labeling for such products includes information necessary for the safe and effective use of the product given the product's anticipated circumstances of use.

For example, this rule applies to certain medical products that enter the SNS as investigational products in addition to medical products in the SNS that are approved,

¹ In the Federal Register of November 18, 2008 (73 FR 68332), FDA issued a technical amendment to reincorporate a regulation that was inadvertently revised by the interim final rule.

licensed, or cleared for marketing.² Labels on investigational products ordinarily would not contain all elements required on licensed, approved, or cleared product labels. Certain information, such as expiration dates, warnings for users, license numbers of manufacturers and other information, may not be available or finalized for an investigational product, and thus could not be included on a container label if the investigational product was added to the SNS. Prior to the implementation of this rule, when investigational products were ultimately approved for marketing, the products would have been returned to the manufacturer or sent to relabelers for relabeling, a potentially time-consuming, costly, and labor-intensive process. Further, requiring relabeling of such investigational products after approval, licensure or clearance could adversely affect the safety, effectiveness, or availability of the products. This rule allows the appropriate FDA Center Director to grant an exception or alternative to the relevant labeling requirements to enable the immediate use of a product in the event of a public health emergency.

For these reasons, as explained in the interim final rule and the following section of this document, this rule allows FDA Center Directors to grant exceptions or alternatives to certain labeling requirements not explicitly required by statute for medical products that are or will be included in the SNS.

II. Comments on the Interim Final Rule and FDA Responses

We received 7 comments on the proposed rule. These comments were received from hospitals, biologics manufacturers, law firms, other government agencies, and other interested persons. To make it easier to identify comments and our responses, the word

² As noted in the preamble to the interim final rule, medical products stockpiled in the SNS may also include products that will ultimately be used in an emergency under section 564 of the FD&C Act (21 U.S.C. 360bbb-3).

“Comment,” in parentheses, will appear before the comment’s description, and the word “Response,” in parentheses, will appear before our response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment’s value or importance or the order in which it was received. Certain comments were grouped together because the subject matter of the comments was similar.

(Comment 1) One comment applauded the efforts put forth by the Agency to provide industry with the opportunity for exceptions or alternatives to FDA labeling requirements for products held by the SNS. The comment also recognized the importance of facilitating rapid access to large quantities of medical products in the event of an act of terrorism or natural disaster. Another comment expressed general agreement with the interim final rule.

(Response) We appreciate these comments in support of the rule. Congress mandated the development of a SNS to provide for the emergency health security of the United States in the event of a bioterrorist attack or other public health emergency (section 319F-2(a) of the Public Health Service Act (the PHS Act) (42 U.S.C. 247d-6(b))). By providing a legal mechanism for addressing certain labeling issues associated with medical products in the SNS without compromising their safety, effectiveness, or availability for use in an emergency, this rule is designed to help enable the rapid deployment of medical countermeasures stored in the SNS in the event of such an emergency.

(Comment 2) A number of comments responded to FDA’s solicitation for comments as to whether the scope of the rule should be amended to include medical

products in other Federal, State, and local stockpiles. One comment suggested that FDA expand the rule to include medical products stored in hospitals. Another comment suggested that the interim final rule should be extended to medical products stored in the Department of Defense stockpiles. Yet another comment requested that the scope of the rule not be extended to medical products in other Federal, State, or local stockpiles because extending the scope of the rule would most likely result in manufacturers seeing a high influx of requests for exceptions or alternatives to labeling requirements under the rule. Finally, a comment expressed general concern that the interim final rule is flawed and therefore should not be extended to other stockpiles.

(Response) We appreciate the comments received in response to our solicitation. We have considered the issue, including the points raised in these comments, and have decided not to extend the rule to other Federal, State, and local stockpiles. With respect to the comment that the scope of the rule should be extended to medications stored in hospitals, we note that the SNS was created by statute to maintain medical products under centralized control. Centralized control of the stockpile assures that appropriate products are selected for inclusion in the SNS and that they are then stored under appropriate conditions. Centralized control also provides for efficient distribution in the event of a public health emergency.

In response to the comment expressing concern that extending the rule to include additional medical products in other Federal, State, or local stockpiles would cause a high influx of requests for exceptions or alternatives to the labeling requirements specified in the rule, we recognize that extending the rule to other stockpiles may result in a high influx of requests and further note our concern that such requests would relate to products

outside the control of SNS oversight. We reiterate that medical products are stockpiled in the SNS under centralized control to provide for efficient distribution in the event of a bioterrorist attack or other public health emergency, and this centralized control helps ensure that adequate procedures are followed for inventory management and accounting, and for the physical security of the stockpile. Accordingly, at this time, we decline to expand the scope of the final rule to apply to medical products in other Federal, State, and local stockpiles. Additionally, we note our disagreement with the comment that the interim final rule is generally flawed. As mandated by Congress, the SNS was created to provide for the emergency health security of the United States in the event of a public health emergency such as a bioterrorist attack. The interim final rule is necessary to give FDA Center Directors the ability to grant exceptions or alternatives to certain regulatory labeling requirements that could adversely affect the safety, effectiveness, or availability of medical products that are or will be included in the SNS in the event of a public health emergency.

(Comment 3) There were two comments regarding those provisions of the interim final rule which allow SNS officials, or any entity that manufactures (including labeling, packing, repackaging, or relabeling), distributes, or stores the medical products to submit a request for an exception or alternative to the labeling requirements specified in the rule. One comment expressed concern that the rule permitted a SNS official to apply for alternative labeling without the consent of the product license holder. The comment acknowledged that there may be situations that could require a SNS official to apply for a labeling change without the license holder's consent, such as if a license holder went out of business, but stated that in all other cases only the product license

holder (or, in the case of an investigational product, the anticipated biologics license application (BLA) or new drug application (NDA) holder) should be permitted to request an exception or alternative to the labeling requirements specified in the rule. The comment further suggested that any request by a SNS official for an exception or alternative to the labeling requirements specified in the rule should be accompanied by the written concurrence of the product license holder.

Similarly, another comment requested that the rule be amended to allow only the product license holder or the sponsor of the investigational new drug application (IND) to submit a request for a labeling exception or alternative. The comment further requested that the rule be amended to require SNS officials to first submit a request for an alternative or exception to the labeling requirements specified in the rule to the product license holder or IND sponsor for its concurrence prior to submitting the request to FDA, and that the license holder or IND sponsor be required to concur with the request prior to SNS officials forwarding the request to FDA.

(Response) The interim final rule allows for drug, biologic, and device application holders, or sponsors of INDs or investigational device exemptions (IDEs), to submit requests for labeling exceptions or alternatives. Our experience to date with respect to the interim final rule has been that BLA holders or applicants or sponsors of INDs have submitted all of the requests received for labeling exceptions or alternatives with the concurrence of SNS officials. We continue to anticipate that many, if not all, of the requests submitted under this rule will be submitted by manufacturers with the concurrence of SNS officials prior to or at the time a specified lot, batch, or other unit of the product is procured by the SNS, or when an investigational product held in the SNS

has been approved, licensed, or cleared. Nonetheless, we also continue to recognize the need for additional flexibility regarding products stored in the SNS to ensure their availability in the event of a public health emergency. For example, in order to prepare for an emergency, an SNS official or FDA Center Director could determine there is a need for labeling exceptions or alternatives to facilitate the use of a medical countermeasure during an emergency. We note that in this example we anticipate that the exception or alternative required would not result in any actual change to the product labeling, but rather would allow for the use of the product regardless of the current labeling.

Thus, we continue to recognize that it may be necessary to allow government officials, as well as any entity that manufactures (including labeling, packing, repackaging, or relabeling), distributes, or stores the medical product, to request exceptions or alternatives to the labeling requirements specified in this rule to ensure that medical products stored in the SNS are rapidly available for public use.

(Comment 4) A comment suggested that FDA grant or deny a request for an exception or alternative within 30 days from the receipt of any request because such situations may call for rapid turnaround.

(Response) We agree that there may be situations that could call for a rapid turnaround in responding to a request for an exception or alternative. The intent of this rule is to ensure the rapid availability of medical countermeasures in the event of a public health emergency, and FDA will respond to all requests regarding the SNS as rapidly as possible. However, we do not believe that requiring FDA to respond within a set

timeframe without accounting for the variability and complexity of each request would necessarily serve the public health.

(Comment 5) One comment asked what documentation would be provided to the Department of Homeland Security's Customs and Border Protection Agency (CBP) to allow importation of medical products that are the subject of grants of exceptions or alternatives to labeling requirements.

(Response) This rule has no effect on the information that must be submitted to CBP for imported medical products. That documentation remains unchanged. FDA and CBP will be able to make appropriate determinations regarding products for which exceptions or alternatives have been granted without additional information at the time of entry.

(Comment 6) A comment stated that while the rule appears to permit only minor and technical labeling changes, it appears to be intended to permit FDA to make additional labeling changes based on information that becomes available to FDA after the initial label approval. The comment argued that a change to previously approved labels based on information not previously available alters the conditions under which a product may be sold and may affect the product's value without appropriate compensation to the manufacturer. Furthermore, the comment expressed a general concern that such actions by the government may violate the Constitution's Due Process and Takings provisions. The comment further argued that even if such actions did not rise to the level of Constitutional violations, they would be disincentives to industry developing products with uses covered by the SNS. Finally, the commenter was concerned that FDA may

require a manufacturer of investigational products to add language to the outer package labeling of its product in the SNS after the product is licensed, approved, or cleared.

(Response) The concerns expressed in the comment are unfounded. We do not agree that FDA's grant of an exception or alternative to certain FDA labeling requirements under the rule would adversely affect a product's value. This rule applies to medical products that are or will be held in the SNS only. The purpose of the rule is to provide for exceptions or alternatives to certain regulatory requirements if compliance with the requirements could adversely affect the safety, effectiveness, or availability of these products. Therefore, we would anticipate that this rule could encourage, as opposed to discourage, the procurement of medical products by the SNS.

We reiterate that this rule is narrowly drafted to create necessary exceptions or alternatives to specified labeling requirements to ensure that medical products stored in the SNS are available for public use in the event of an emergency. To date, we have received six requests for exceptions or alternatives to labeling requirements, all of which have been initiated by BLA holders or applicants or sponsors of IND applications, with the concurrence of SNS officials. Our experience to date is that this rule does not create disincentives to participation in the SNS, and we note that the comment did not contain any data or information to substantiate this concern. Furthermore, to the extent that the comment is arguing that this rule violates the Due Process and Takings clauses of the Constitution by affecting a product's value without appropriate compensation to the manufacturer, as discussed previously, we disagree. As we have explained, this rule will not adversely affect the value of a product. We do not believe that this rule in any way violates the Constitution.

(Comment 7) One comment expressed concern that relabeling a product suggests product manipulation. The comment stated that over labeling or relabeling creates the possibility for error, damage to the product and potential confusion by the SNS and, ultimately, for the user for whom the product is intended. Further, any of these possibilities may increase product liability exposure for the manufacturer.

(Response) The concerns expressed in the comment are unfounded. As stated in the preamble to the interim final rule, we recognize that relabeling is a potentially time-consuming, costly, and labor-intensive process that could possibly cause product mishandling, sabotage or diversion, or could cause products to be unavailable for dispensing in the event of an emergency. Accordingly, this rule is specifically designed to allow FDA Center Directors to grant exceptions or alternatives to certain labeling requirements for medical products in the SNS to mitigate the need for relabeling. We also note that since the development of the SNS, manufacturers, in conjunction with FDA, the Centers for Disease Control and Prevention/SNS officials and the Department of Health and Human Services/Biomedical Advanced Research and Development Authority, have developed innovative labeling mechanisms for certain products through which relabeling an investigative product requires minimal manipulation post-licensure (e.g., “zipper” labels or “tear-off” labels on the actual product container).

Regarding the product liability concern, this rule does not authorize the use of unapproved products, or of approved products for unapproved uses in an emergency. This rule instead permits a Center Director to authorize an exception or alternative from certain labeling requirements. Notably, with regard to other product liability concerns the commenter may have, the Public Readiness and Emergency Preparedness (PREP) Act is

intended to address tort liability for manufacturers in such circumstances (42 U.S.C. 247d-6(d)).

(Comment 8) A comment stated that the rule would appear to place burdens on a manufacturer. For example, the comment states that the rule does not exempt a sponsor from the requirement that it include in the company's annual report to FDA changes in labeling even when the government initiated the change without input from the manufacturer. The comment suggests that therefore, the company will need to track the activities of the SNS after the product has been distributed.

(Response) FDA clarifies that under 21 CFR 201.26(e), a sponsor or applicant would only have to report a grant of a request for an exception or alternative of labeling requirements if the sponsor or applicant requested the change. We also note that we expect that in the majority of cases, this exception or alternative would be granted during the product approval process. Accordingly, FDA does not expect this rule to impose burdensome reporting requirements on manufacturers.

III. Legal Authority

In this final rule, FDA is amending regulations pertaining to the content and format of medical product labeling. The provisions of this rule allow FDA to grant exceptions or alternatives to certain of those labeling requirements. The labeling regulations to which exceptions or alternatives are permitted under this rule were issued by FDA under authority of the FD&C Act and the PHS Act to mandate particular ways that firms must satisfy the broad requirements and prohibitions in those statutes, such as the prohibition on false and misleading drug and device labeling. As described in section II of this document, and in the interim final rule, FDA has determined that circumstances

may arise in which compliance with those regulatory mandates could adversely affect the safety, effectiveness, or availability of certain medical products that are or will be included in the SNS. Moreover, due to the unique nature of the SNS, those products could deviate from particular mandates of existing labeling regulations without violating the broad statutory requirements and prohibitions in the FD&C Act and the PHS Act. For those reasons, FDA is exercising its authority to regulate labeling by modifying the existing regulations in a way that allows exceptions or alternatives for medical products that are or will be included in the SNS.

As explained in the interim final rule, FDA has various sources of authority to issue labeling regulations, including, for example, sections 201(n), 502(a), and 701(a) of the FD&C Act (21 U.S.C. 321(n), 352(a), and 371(a)) for drugs (including biological products) and devices, and sections 351(a)(1)(A) and 351(a)(2)(A) of the PHS Act (42 U.S.C. 262(a)(1)(A) and (a)(2)(A)) for biological products. In addition, as more fully discussed in the interim final rule, FDA has concluded that exceptions or alternatives granted under this rule will not render products misbranded due to the additional safeguards and conditions that may be required when an exception or alternative is granted, as well as the unique storage, deployment and distribution considerations essential to the SNS.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory

alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The analysis of costs and benefits of available regulatory alternatives contained in the interim final rule (72 FR 73589 at 73596) is adopted without change in this final rule. By now reaffirming that interim final rule, FDA has not imposed any new requirements. Therefore, there are no additional costs and benefits associated with this final rule.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule does not make any changes to the interim final rule or our analysis included therein, the Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

V. The Paperwork Reduction Act

Sections 201.26(b), 610.68(b), 801.128(b), and 809.11(b) of this final rule contain information collection requirements that were submitted for review and approval to the Director of the Office of Management and Budget (OMB), as required by section 3507(d) of the Paperwork Reduction Act of 1995. The information collection requirements were approved and assigned OMB control number 0910-0614 (expires August 31, 2014).

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(k) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

In the Federal Register of October 5, 2011 (76 FR 61565), FDA published a notification of preemption review, which was conducted in response to a memorandum from the President that directed Federal Agencies to review recently issued regulations to ensure that any statements concerning preemption can be justified under legal principles governing preemption, including those outlined in Executive Order 13132. In this notification, FDA announced its determination that the preamble to the interim final rule referred to statements concerning preemption that are not justified under legal principles governing preemption. FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132 and has determined that this rule is consistent with the Executive Order. Section 4(a) of this Executive Order requires agencies to “construe * * * a Federal statute to preempt State law only where the statute

contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” In this rule, FDA is adopting as a final rule regulations permitting FDA Center Directors to grant exceptions or alternatives to certain regulatory labeling requirements applicable to medical products that are or will be included in the SNS. Certain State requirements regarding the format and content of nonprescription drug labeling and/or labeling of approved medical devices may be subject to the express preemption provisions in section 751 of the FD&C Act (21 U.S.C. 379r) (nonprescription drugs) and section 521 of the FD&C Act (21 U.S.C. 360k) (approved medical devices). We also note that even where an express preemption provision is not applicable, implied preemption may arise.

Accordingly, the interim final rule amending 21 CFR parts 201, 312, 314, 601, 610, 801, 807, 809, 812, and 814 which was published at 72 FR 73589 on December 28, 2007, is adopted as a final rule without change.

Dated: February 1, 2012

Leslie Kux,

Acting Assistant Commissioner for Policy.